

**CLAIMS**

What is claimed is:

1. A process for preparing (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol in its free base, its salt form, or both, which process comprises a dynamic kinetic resolution by equilibrating the two chiral centers of (+/-)-(2R\*, 3R\*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol.
2. A process according to claim 1 which process comprises the steps of:
  - (1) treating (+/-)-(2R\*,3R\*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol dissolved in a solvent with at least one base to give a solution having a pH of about pH 8 to a pH of about pH 12;
  - (2) adding at least 0.5 equivalent of a chiral acid with stirring while maintaining the pH of the solution between about pH 8 to about pH 12 with additional base;
  - (3) adding seed crystals of the desired chiral acid salt of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol with stirring; and
  - (4) adding at least 0.5 equivalent of additional chiral acid at pH 8 to pH 12, with additional base added as needed, and then adjusting the pH of the mixture until the pH reaches about pH 6 to pH 8 with acid.
3. The process according to claim 2, wherein the chiral acid is a protected or unprotected chiral tartaric acid.
4. The process according to claim 2, wherein the chiral acid is selected from the group consisting of L-tartaric acid, D-tartaric acid, (-)-(R, R)-di-p-benzoyl-L-tartaric acid, (+)-(S, S)-di-p-benzoyl-D-tartaric acid, (-)-(R, R)-di-p-toluoyl-L-tartaric acid, (+)-(S, S)-di-p-toluoyl-D-tartaric acid, and (-)-(1R)-10-camphorsulfonic acid, (+)-(1S)-10-camphorsulfonic acid D-malic acid, L-malic acid, D-mandelic acid or L-mandelic acid.

5. The process according to claim 4, wherein the chiral acid is (-)-(R, R)-di-p-toluoyl-L-tartaric acid.
6. The process according to claim 2, wherein the chiral acid is a substituted or unsubstituted chiral camphorsulphonic acid.
7. The process according to claim 6, wherein the chiral camphorsulphonic acid is selected from the group consisting of (-)-(1R)-10-camphorsulphonic acid and (+)-(1S)-10-camphorsulfonic acid.
8. The process according to claim 2, wherein the base is an inorganic base or an organic base.
9. The process according to claim 8, wherein the inorganic base is at least one selected from the group consisting of alkali metal hydrogen carbonates, alkali metal carbonates, alkali metal hydroxides, and ammonium hydroxide.
10. The process of claim 9 wherein said alkali metal hydrogen carbonates are selected from the group consisting of sodium hydrogen carbonate and potassium hydrogen carbonate; and wherein the alkali metal carbonates are selected from the group consisting of sodium carbonate and potassium carbonate.
11. The process according to claim 8, wherein the organic base is at least one selected from the group consisting of aliphatic amine bases and aromatic amine bases.
12. The process according to claim 11, wherein the organic base is triethylamine.

13. The process according to claim 2, wherein the solvent is a protic solvent.
14. The process according to claim 13, wherein said protic solvent is at least one selected from the group consisting methanol and ethanol.
15. The process according to claim 2, wherein the seed crystal is a (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol (-)-(R, R)-di-p-toluoyl-L-tartaric acid salt.
16. The process according to claim 2, wherein said at least 1.0 equivalent of a chiral acid is added slowly over a period of about 1 to about 4 hours.
17. The process according to claim 2, wherein said additional chiral acid is added slowly over a period of about 1 to about 4 hours.
18. The process according to claim 2, wherein said solution or mixture of step (1) has a pH of about pH 9 to about pH 11.
19. The process according to claim 2, wherein said solution or mixture of step (2) has a pH of about pH 9 to about pH 11.
20. The process according to claim 2, wherein said solution or mixture of step (4) has a final pH of about pH 6.5 to about pH 7.5.
21. The process according to claim 2, further comprising the step of:
  - (5) isolating a solid acid salt of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol from said solution or mixture of step (4).

22. The process according to claim 21, wherein said isolation is performed using a sintered glass filter funnel, a Gooch filter, a pan filter, and a Rosemund filter.
23. The process according to claim 21, further comprising the step of:
  - (6) converting said solid acid salt of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol of step (5) into (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol free base.
24. The process according to claim 23, wherein said solid acid salt is converted into its free base form of the acid salt with a base.
25. The process according to claim 24, wherein said base is a strong base in an excess amount.
26. The process according to claim 25, wherein said base is selected from the group consisting of ammonium hydroxide, potassium hydroxide, sodium hydroxide, and mixtures thereof in water.
27. The process according to claim 23, further comprising the step of:
  - (7) converting the (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol free base of step (6) into a (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol acid salt.
28. The process according to claim 27, wherein said free base is converted into said hydrochloride salt by addition of more than one equivalent of hydrochloric acid and a anti-solvent or by addition of more than one equivalent of hydrogen chloride gas and a anti-solvent, such that the pH of the solution or mixture reaches a pH of about pH 1 to a pH of about pH 2.

29. The process according to claim 28, wherein said solvent is selected from the group consisting of methanol, ethanol, ethyl acetate, isopropyl acetate, acetonitrile, and mixtures thereof; and said anti-solvent is selected from the group consisting of ethyl acetate, isopropyl acetate, ethyl ether, methyl t-butyl ether, and mixtures thereof.
30. The process according to claim 28, further comprising the step of:  
(8) recrystallizing the (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride salt of step (7).
31. The process according to claim 30, wherein said recrystallization of step (8) is performed by polishing filtration and crystallization with one or more organic solvents.
32. The process according to claim 31, wherein said one or more organic solvent is selected from the group consisting of methanol, ethanol, ethyl acetate, isopropyl acetate, and acetonitrile.
33. The process according to claim 27 wherein said acid salt form is selected from the group consisting of
- (i) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride salt;
  - (ii) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrogen sulfate salt;
  - (iii) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrogen phosphate salt;
  - (iv) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol methanesulfonate salt;
  - (v) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol p-toluenesulfonate salt;
  - (vi) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol citrate salt;

- (vii) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol fumarate salt; and
- (viii) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol tartrate salt.

34. A pharmaceutical composition comprising an active ingredient of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, a pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate thereof prepared in accordance with claim 1 together with at least one pharmaceutically acceptable excipient.

35. A method for the treatment of depression, attention deficit hyperactivity disorder, anxiety, obesity, migraine, pain, sexual dysfunction, Parkinson's disease, Alzheimer's disease, seasonal affective disorder, addiction to alcohol, addiction to cocaine, or addiction to nicotine-containing products comprising the oral administration to a mammal of an active ingredient comprising (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof prepared in accordance with claim 1 together with at least one pharmaceutically acceptable excipient.

36. The use of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, a pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate thereof prepared in accordance with claim 1 in the manufacture of a medicament.